WO0170683

Title:
3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

Abstract:

3-Substituted-4-pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof, wherein R<1> represents a C1-C18 alkyl group which may be substituted or a C6-C14 aryl group which may be substituted; R<2> represents a C1-C18 alkyl group which may be substituted or a C7-C20 aralkyl group which may be substituted; and a medicament comprising said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity such as neurodegenerative diseases (e.g. Alzheimer disease) and the like.

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(71) Applicants *(for all designated States except US)*: **MITSUBISHI-TOKYO PHARMACEUTICALS, INC.** [JP/JP]; 2-6, Nihonbashi-honcho 2-chome, Chuo-ku, Tokyo 103-8405 (JP). **SANOFI-SYNTHELABO** [FR/FR]; 174, avenue de France, F-75013 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANDO, Ryoichi** [JP/JP]; Mitsubishi-Tokyo Pharmaceuticals, Inc., Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-0033 (JP). **UEHARA, Fumiaki** [JP/JP]; Mitsubishi-Tokyo Pharmaceuticals, Inc., Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-0033 (JP). **SAITO, Ken-ichi** [JP/JP]; Mitsubishi-Tokyo Pharmaceuticals, Inc., Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-0033 (JP).

(74) Agents: **IMAMURA, Masazumi** et al.; Kyobashi Nisshoku Building, 8th Floor, 8-7, Kyobashi 1-chome, Chuo-ku, Tokyo 104-0031 (JP).

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(54) Title: 3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

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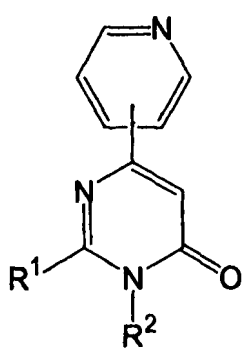


(I)

(57) Abstract: 3-Substituted-4-pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof, wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted or a C_6-C_{14} aryl group which may be substituted; R^2 represents a C_1-C_{18} alkyl group which may be substituted or a C_7-C_{20} aralkyl group which may be substituted; and a medicament comprising said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity such as neurodegenerative diseases (e.g. Alzheimer disease) and the like.

DESCRIPTION

3-SUBSTITUTED-4-PYRIMIDONE DERIVATIVES

Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases mainly caused by abnormal advance of tau protein kinase 1, such as neurodegenerative diseases (e.g. Alzheimer disease) and the like.

Background Art

Alzheimer disease is progressive senile dementia, in which marked cerebral cortical atrophy is observed due to degeneration of nerve cells and decrease of nerve cell number. Pathologically, numerous senile plaques and neurofibrillary tangles are observed in brain. The number of patients has been increased with the increment of aged population, and the disease arises a serious social problem. Although various theories have been proposed, a cause of the disease has not yet been elucidated. Early resolution of the cause has been desired.

It has been known that the degree of appearance of two characteristic pathological changes of Alzheimer disease well correlates to the degree of intellectual dysfunction. Therefore, researches have been conducted from early 1980's to reveal the cause of the disease through molecular level investigations of components of the two pathological changes. Senile plaques accumulate extracellularly, and amyloid β protein has been elucidated as their main component (abbreviated as "Aβ" hereinafter in the specification: Biochem. Biophys. Res. Commun., 120, 855 (1984); EMBO J., 4, 2757 (1985); Proc. Natl. Acad. Sci. USA, 82, 4245 (1985)). In the other pathological change, i.e., the neurofibrillary tangles, a double-helical filamentous

substance called paired helical filament (abbreviated as "PHF" hereinafter in the specification) accumulate intracellularly, and tau protein, which is a kind of microtubule-associated protein specific for brain, has been revealed as its main component (Proc. Natl. Acad. Sci. USA, 85, 4506 (1988); Neuron, 1, 827 (1988)).

Furthermore, on the basis of genetic investigations, presenilins 1 and 2 were found as causative genes of familial Alzheimer disease (Nature, 375, 754 (1995); Science, 269, 973 (1995); Nature. 376, 775 (1995)), and it has been revealed that presence of mutants of presenilins 1 and 2 promotes the secretion of A β (Neuron, 17, 1005 (1996); Proc. Natl. Acad. Sci. USA, 94, 2025 (1997)). From these results, it is considered that, in Alzheimer disease, A β abnormally accumulates and agglomerates due to a certain reason, which engages with the formation of PHF to cause death of nerve cells. It is also expected that extracellular outflow of glutamic acid and activation of glutamate receptor responding to the outflow may possibly be important factors in an early process of the nerve cell death caused by ischemic cerebrovascular accidents (Sai-shin Igaku [Latest Medicine], 49, 1506 (1994)).

It has been reported that kainic acid treatment that stimulates the AMPA receptor, one of glutamate receptor, increases mRNA of the amyloid precursor protein (abbreviated as "APP" hereinafter in the specification) as a precursor of A β (Society for Neuroscience Abstracts, 17, 1445 (1991)), and also promotes metabolism of APP (The Journal of Neuroscience, 10, 2400 (1990)). Therefore, it has been strongly suggested that the accumulation of A β is involved in cellular death due to ischemic cerebrovascular disorders. Other diseases in which abnormal accumulation and agglomeration of A β are observed include, for example, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, Lewy body disease (Shin-kei Shinpo [Nerve Advance], 34, 343 (1990); Tanpaku-shitu Kaku-san Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)) and the like. Furthermore, as diseases showing neurofibrillary tangles due to the PHF accumulation, examples include

progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease and the like (Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 36, 2 (1991); Igaku no Ayumi [Progress of Medicine], 158, 511 (1991); Tanpakushitu Kakusan Koso [Protein, Nucleic Acid, Enzyme], 41, 1476 (1996)).

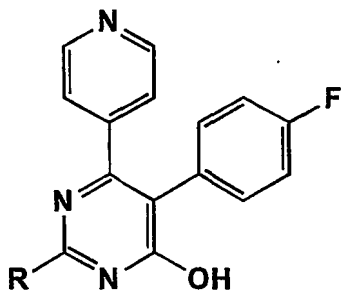
The tau protein is generally composed of a group of related proteins that forms several bands at molecular weights of 48-65 kDa in SDS-polyacrylamide gel electrophoresis, and it promotes the formation of microtubules. It has been verified that tau protein incorporated in the PHF in the brain suffering from Alzheimer disease is abnormally phosphorylated compared with usual tau protein (J. Biochem., 99, 1807 (1986); Proc. Natl. Acad. Sci. USA, 83, 4913 (1986)). An enzyme catalyzing the abnormal phosphorylation has been isolated. The protein was named as tau protein kinase 1 (abbreviated as "TPK1" hereinafter in the specification), and its physicochemical properties have been elucidated (Seikagaku [Biochemistry], 64, 308 (1992); J. Biol. Chem., 267, 10897 (1992)). Moreover, cDNA of rat TPK1 was cloned from a rat cerebral cortex cDNA library based on a partial amino acid sequence of TPK1, and its nucleotide sequence was determined and an amino acid sequence was deduced (Japanese Patent Un-examined Publication [Kokai] No. 6-239893/1994). As a result, it has been revealed that the primary structure of the rat TPK1 corresponds to that of the enzyme known as rat GSK-3 β (glycogen synthase kinase 3 β, FEBS Lett., 325, 167 (1993)).

It has been reported that A β, the main component of senile plaques, is neurotoxic (Science, 250, 279 (1990)). However, various theories have been proposed as for the reason why A β causes the cell death, and any authentic theory has not yet been established. Takashima et al. observed that the cell death was caused by A β treatment of fetal rat hippocampus primary culture system, and then found that the

TPK1 activity was increased by A β treatment and the cell death by A β was inhibited by antisense of TPK1 (Proc. Natl. Acad. Sci. USA, 90, 7789 (1993); Japanese Patent Un-examined Publication [Kokai] No. 6-329551/1994).

In view of the foregoing, compounds which inhibit the TPK1 activity may possibly suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death in the Alzheimer disease, thereby cease or defer the progress of the disease. The compounds may also be possibly used as a medicament for therapeutic treatment of ischemic cerebrovascular disorder, Down syndrome, cerebral amyloid angiopathy, cerebral bleeding due to Lewy body disease and the like by suppressing the cytotoxicity of A β. Furthermore, the compounds may possibly be used as a medicament for therapeutic treatment of neurodegenerative diseases such as progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration and frontotemporal dementia.

As structurally similar compounds to the compounds of the present invention represented by formula (I) described later, compounds represented by the following formula (A) are known:



(A)

wherein R represents 2,6-dichlorobenzyl group, 2-(2-chlorophenyl)ethylamino group, 3-phenylpropylamino group, or 1-methyl-3-phenylpropylamino group (WO98/24782).

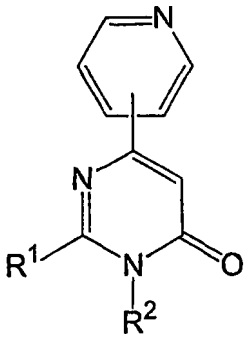
The compounds represented by formula (A) are characterized to have 4-fluorophenyl group at the 5-position of the pyrimidine ring and a hydroxy group at the 4-position, and not falling within the scope of the present invention. Moreover, main pharmacological activity of the compounds represented by formula (A) is anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) are useful as a TPK1 inhibitor or a medicament for therapeutic treatment of neutodegenerative diseases, and therefore, their pharmacological activities are totally different to each other.

Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases such as Alzheimer disease and the like. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables radical prevention and/or treatment of the diseases such as Alzheimer disease by inhibiting the TPK1 activity to suppress the neurotoxicity of A β and the formation of the PHF and by inhibiting the death of nerve cells.

In order to achieve the foregoing object, the inventors of the present invention conducted screenings of various compounds having inhibitory activity against the phosphorylation of TPK1. As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases. The present invention was achieved on the basis of these findings.

The present invention thus provides 3-substituted-4-pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



(I)

wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted or a C_6-C_{14} aryl group which may be substituted;

R^2 represents a C_1-C_{18} alkyl group which may be substituted or a C_7-C_{20} aralkyl group which may be substituted.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; and cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors. As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism,

pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Pick's disease, corticobasal degeneration, frontotemporal dementia, retinopathies and glaucoma; and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives. The present invention further provides an inhibitor of tau protein kinase 1 comprising as an active ingredient a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.

According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of diseases caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

Best Mode for Carrying Out the Invention

The alkyl group used herein may be either linear or branched. The C_1-C_{18} alkyl group represented by R^1 may be, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, or a linear or branched heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group or octadecyl group. In the

specification, when a functional group is defined as "which may be substituted" or "optionally substituted", the number of substituents as well as their types and substituting positions are not particularly limited, and when two or more substituents are present, they may be the same or different.

When the C_1-C_{18} alkyl group represented by R^1 has one or more substituents A, the alkyl group may have one or more substituents A selected form the group consisting of a C_3-C_8 cycloalkyl group such as cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group; a C_6-C_{10} aryl group such as phenyl group, 1-naphthyl group, and 2-naphthyl group; a C_3-C_8 cycloalkyloxy group such as cyclopropyloxy group, cyclobutyloxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group; fluorenyl group; a C_1-C_5 alkoxyl group such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, tert-butoxy group, pentyloxy group, and isopentyloxy group; a C_7-C_{20} aralkyloxy group such as benzyloxy group, phenylethyloxy group, phenylpropyloxy group, phenylbutyloxy group, naphthylmethyloxy group, naphthylethyloxy group, naphthylpropyloxy group, and naphthylbutyloxy group; a C_6-C_{14} aryloxy group such as phenoxy group, and naphthoxy group; a C_1-C_5 alkylthio group such as methylthio group, ethylthio group, propylthio group, butylthio group, and pentylthio group; a C_7-C_{20} aralkylthio group such as benzylthio group, phenylethylthio group, phenylpropylthio group, phenylbutylthio group, naphthylmethylthio group, naphthylethylthio group, naphthylpropylthio group, and naphthylbutylthio group; a C_6-C_{14} arylthio group such as phenylthio group, and naphthylthio group; a C_1-C_5 alkylsulfonyl group such as methanesulfonyl group, ethanesulfonyl group, propanesulfonyl group, butanesulfonyl group, and pentanesulfonyl group; a C_6-C_{14} arylsulfonyl group such as phenylsulfonyl group, and naphthylsulfonyl group; a halogen atom such as fluorine atom, chlorine atom, bromine atom, and iodine atom; a C_1-C_5 halogenated alkyl group such as

trifluoromethyl group; hydroxyl group; cyano group; nitro group; formyl group; a C_2-C_6 alkylcarbonyl group such as acetyl group, propionyl group, butyryl group, and valeryl group; amino group; a C_1-C_5 monoalkylamino group such as methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group, and isopentylamino group; a C_2-C_{10} dialkylamino group such as dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group, and diisopropylamino group; and a residue of heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10, for example, furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, phthalazine ring, naphtylidine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

When an aryl group or a heterocyclic group is present as a substituent, the group may have one or more substituents B selected form the group consisting of a C_1-C_{18} alkyl group such as methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isopentyl

group, neopentyl group, 1,1-dimethylpropyl group, hexyl group, isohexyl group, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, and octadecyl group; a C_7-C_{20} aralkyl group such as benzyl group, phenylethyl group, phenylpropyl group, phenylbutyl group, naphthylmethyl group, naphthylethyl group, and naphthylpropyl group, naphthylbutyl group; and the aforementioned substituent A.

Examples of the C_6-C_{14} aryl group represented by R^1 include, for example, phenyl group, naphthyl group, and the like. These groups may have one or more substituents B.

As the optionally substituted C_1-C_{18} alkyl group which is represented by R^2, such as those explained as to R^1 may be used.

Examples of the C_7-C_{20} aralkyl group represented by R^2 include, for example, benzyl group, phenylethyl group, phenylpropyl group, phenylbutyl group, naphthylmethyl group, naphthylethyl group, naphthylpropyl group, naphthylbutyl group and the like. These groups may have one or more substituents B.

R^1 may preferably a C_1-C_{18} alkyl group which is substituted by amino group, a C_1-C_5 monoalkylamino group, a C_2-C_{10} dialkylamino group, hydroxyl group or phenyl group which may be substituted; or phenyl group which may be substituted.

More preferably, R^1 may be a C_1-C_{10} alkyl group which is substituted by amino group, a C_1-C_5 monoalkylamino group, a C_2-C_{10} dialkylamino group or phenyl group which may be substituted by a halogen atom, a C_1-C_5 alkyl group or a C_1-C_5 alkoxyl group.

R^2 may preferably be a C_1-C_{10} alkyl group which may be substituted by amino group, a C_1-C_5 monoalkylamino group, or a C_2-C_{10} dialkylamino group; or C_7-C_{20} aralkyl group which may be substituted.

More preferably, R^2 may be a C_1-C_{10} alkyl group which may be substituted by amino group, a C_1-C_5 monoalkylamino group, or a C_2-C_{10} dialkylamino group; or

benzyl group which may be substituted.

The pyridyl group bound to the pyrimidine ring may be any one of 2-pyridyl, 3-pyridyl or 4-pyridyl group. Among them, 4-pyridyl group may be preferred and unsubstituted-4-pyridyl group be more preferred.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine, δ -hydroxylysine, and arginine. When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and glutamic acid.

In addition to the 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The 3-substituted-4-pyrimidone derivatives represented by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers of pure form, any mixtures of stereoisomers,

racemates and the like fall within the scope of the present invention

Examples of preferred compounds of the present invention are shown in the table below. However, the scope of the present invention is not limited by the following compounds. The compounds specifically disclosed in the examples of the present specification are also preferred according to the present invention, as well as those described below.

Table-1

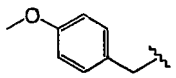
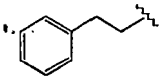
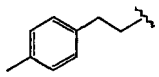
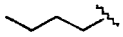
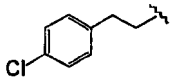
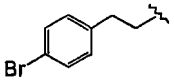
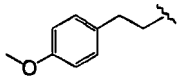
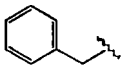
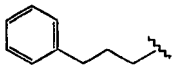
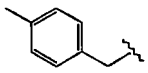
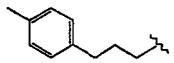
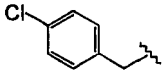
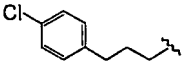
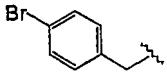
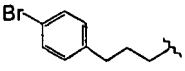
Compound No.	R^1	R^2	Compound No.	R^1	R^2
1	CH_3	CH_3	11		CH_3
2	CH_2CH_3	CH_3	12		CH_3
3		CH_3	13		CH_3
4		CH_3	14		CH_3
5		CH_3	15		CH_3
6		CH_3	16		CH_3
7		CH_3	17		CH_3
8		CH_3	18		CH_3
9		CH_3	19		CH_3
10		CH_3	20		CH_3

Table-1 (continued)

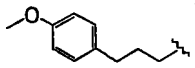
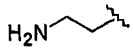
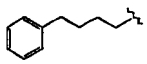
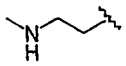
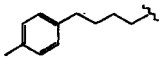
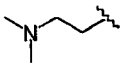
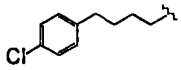
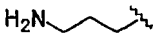
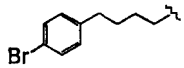
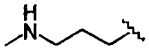
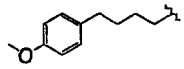
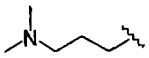
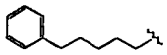
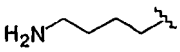
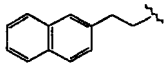
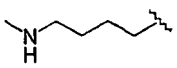
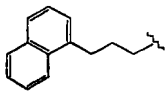
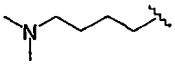
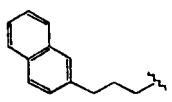
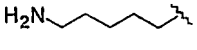
Compound No.	R^1	R^2	Compound No.	R^1	R^2
21		CH_3	31		CH_3
22		CH_3	32		CH_3
23		CH_3	33		CH_3
24		CH_3	34		CH_3
25		CH_3	35		CH_3
26		CH_3	36		CH_3
27		CH_3	37		CH_3
28		CH_3	38		CH_3
29		CH_3	39		CH_3
30		CH_3	40		CH_3

Table-1 (continued)

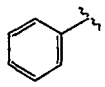
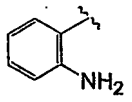
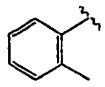
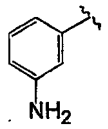
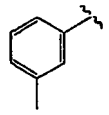
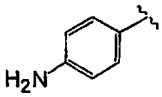
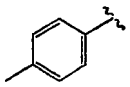
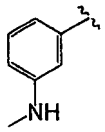
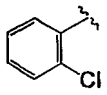
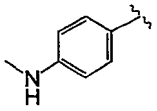
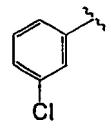
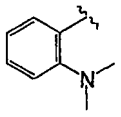
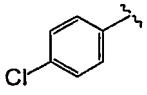
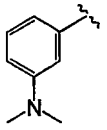
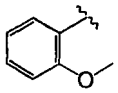
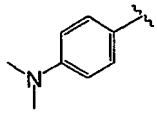
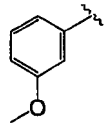
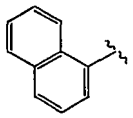
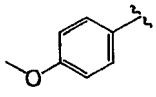
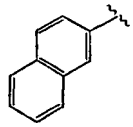
Compound No.	R^1	R^2	Compound No.	R^1	R^2
41		CH_3	51		CH_3
42		CH_3	52		CH_3
43		CH_3	53		CH_3
44		CH_3	54		CH_3
45		CH_3	55		CH_3
46		CH_3	56		CH_3
47		CH_3	57		CH_3
48		CH_3	58		CH_3
49		CH_3	59		CH_3
50		CH_3	60		CH_3

Table-1 (continued)

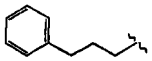
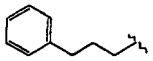
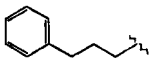
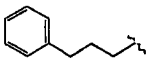
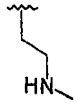
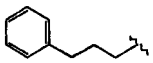
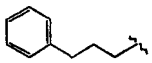
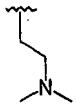
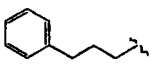
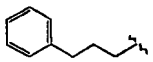
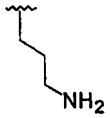
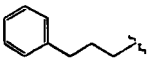
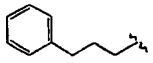
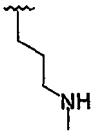
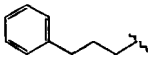
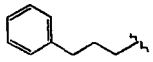
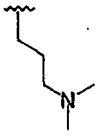
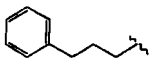
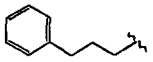
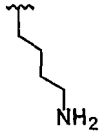
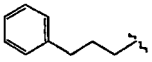
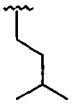
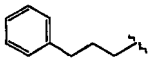
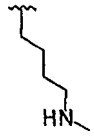
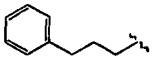
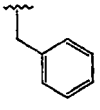
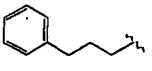
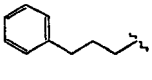
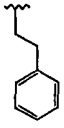
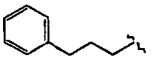
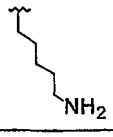
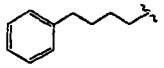
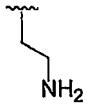
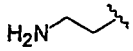
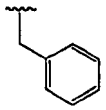
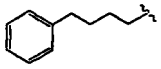
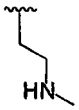
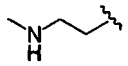
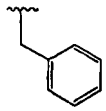
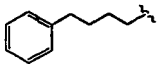
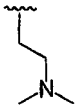
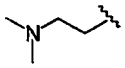
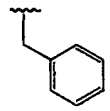
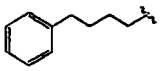
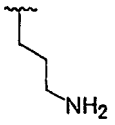
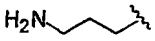
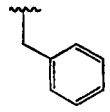
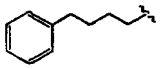
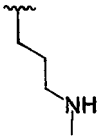
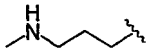
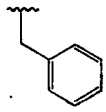
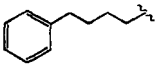
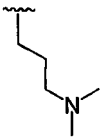
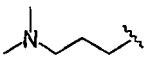
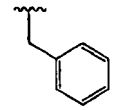
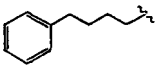
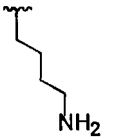
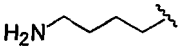
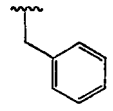
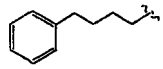
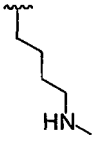
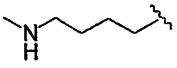
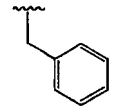
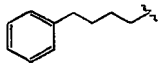
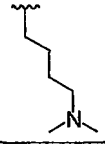
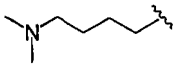
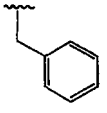
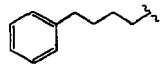
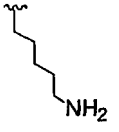
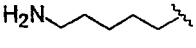
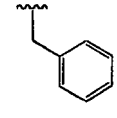
Compound No.	R^1	R^2	Compound No.	R^1	R^2
61		CH_2CH_3	71		
62			72		
63			73		
64			74		
65			75		
66			76		
67			77		
68			78		
69			79		
70			80		

Table-1 (continued)

Compound No.	R^1	R^2	Compound No.	R^1	R^2
81			91		
82			92		
83			93		
84			94		
85			95		
86			96		
87			97		
88			98		
89			99		
90			100		

Particularly preferred compounds of the present invention represented by formula (I) include:

3-methyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-ethyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

2-(3-phenylpropyl)- 3-propyl-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-benzyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-aminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-methylaminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-dimethylaminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

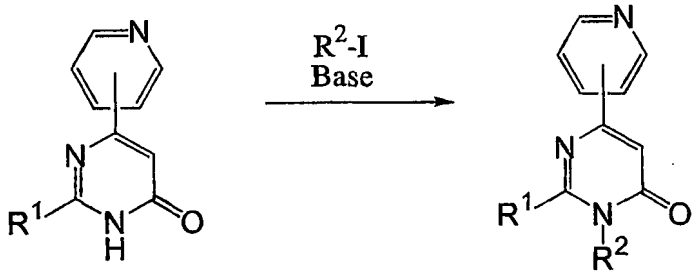
3-(3-aminopropyl)-2-(4-phenylbutyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-aminopropyl)-2-(3-(2-methoxyphenyl)propyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-methyl-2-(3-hydroxy-3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

or salts thereof, or solvates thereof or hydrates thereof.

The 3-substituted-4-pyrimidone compounds represented by the aforementioned formula (I) can be prepared, for example, according to the method explained below.



(II) (I)

(In the above scheme, definitions of R^1 and R^2 are the same as those already described.)

The 3-unsubstituted pyrimidone represented by the above formula (II), which is prepared easily by a similar method described in the patent (toku-gan-hei 10-271277), is allowed to react with the alkyl iodide represented by the formula R^2-I

in the presence of a base such as sodium hydride, 1,8-diazabicyclo[5,4,0]undec-7-en, triethylamine, diisopropylethylamine, potassium hydroxide, sodium hydroxide potassium carbonate, sodium carbonate, and the like.

Examples of a solvent include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbonic solvents such as benzene, toluene, xylene; halogenated hydrocarbonic solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetoaminde, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used so as to be suitable to a base used, and the reaction may be carried out for 1 minute to 14 days at a suitable temperature ranging from -20℃ to 100℃ under nitrogen or argon atmosphere or in under ordinary air. In the above reaction, protection or deprotection of a functional group may sometimes be necessary. A suitable protective group can be chosen depending on the type of a functional group, and a method described in the literature may be applied as experimental procedures.

The compounds of the present invention have inhibitory activity against TPK1, and they inhibit TPK1 activity in Alzheimer disease and the like, thereby suppress the neurotoxicity of A β and the formation of PHF and inhibit the nerve cell death. Accordingly, the compounds of the present invention are useful as an active ingredient of a medicament which radically enables preventive and/or therapeutic treatment of Alzheimer disease. In addition, the compounds of the present invention are also useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases in which abnormal accumulation and agglomeration of A β occur such as ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to solitary cerebral amyloid angiopathy, and Lewy body disease; diseases

showing neurofibrillary tangles due to the PHF accumulation such as progressive supranuclear palsy, subacute sclerosing panencephalitis, postencephalitic parkinsonism, pugilistic encephalosis, Guam parkinsonism-dementia complex and Lewy body disease; Parkinson's disease, tauopathies (e.g., frontotemporoparietal dementia, Pick's disease, corticobasal degeneration, progressive supranuclear palsy) and other dementia including vascular dementia; cerebrovascular accidents (e.g., acute stroke, age related macular degenetarion); traumatic injuries (e.g., brain and spinal cord trauma); peripheral neuropathies; retinopathies and glaucoma; other diseases such as non-insulin dependent diabetes (such as diabetes type II) and obesity; manic depressive illness; schizophrenia; alopecia; and cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se, may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substance may be used in combination. The above pharmaceutical composition may be supplemented with an active ingredient of other medicament for the treatment of Alzheimer disease and the like.

A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine

granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content rations of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for

suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

Examples

The present invention will be explained more specifically with reference to examples. However, the scope of the present invention is not limited to the following examples. The compound number in the examples corresponds to that in the table above.

Example 1: Synthesis of 3-methyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one (Compound No. 17 in Table-1)

To a solution of potassium carbonate (208 mg) in 4 ml of dimethyl sulfoxide and 3 ml of N,N-dimethylformamide, 2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one (437 mg) was added. After the reaction mixture became a clear solution, it was cooled to 0 ℃ and methyl iodide (0.11 ml) was added to it. The obtained reaction mixture was stirred at 0 ℃ for 2 hours, and then water was added to it. The formed precipitates were filtered and washed with water. After the obtained

solid was dried, recrystallization from ethyl acetate gave the desired compound (320 mg), whose yield was 70%.

Melting Point: 144 ℃ .

NMR ($CDCl_3$, δ): 2.23 (m, 2 H), 2.78-2.85 (m, 4 H), 3.50 (s, 3 H), 6.86 (s, 1 H), 7.21-7.33 (m, 5 H), 7.83 (d, J = 6.1 Hz, 2 H), 8.72 (d, J = 6.1 Hz, 2 H).

Compounds of Example 2 to 5 were synthesized in a similar manner to that in Example 1. Physical properties of the compounds are shown below.

Example 2: Synthesis of 3-ethyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one (Compound No. 61 in Table-1)

Melting Point: 111-113 ℃.

NMR ($CDCl_3$, δ): 1.28 (t, J = 6.6 Hz, 3 H), 2.27 (m, 2 H), 2.80-2.86 (m, 4 H), 4.04 (q, J = 6.6 Hz, 2 H), 6.84 (s, 1 H), 7.20-7.35 (m, 5 H), 7.83 (dd, J = 4.5 Hz, 1.8 Hz, 2 H), 8.72 (dd, J = 4.5 Hz, 1.8 Hz, 2H).

Example 3: Synthesis of 2-(3-phenylpropyl)- 3-propyl-6-(4-pyridyl)-3*H*-pyrimidin-4-one (Compound No. 62 in Table-1)

Melting Point: 74-75 ℃.

NMR ($CDCl_3$, δ): 0.94 (t, J = 7.5 Hz, 3 H), 1.67 (m, 2 H), 2.25 (m, 2 H), 2.78-2.85 (m, 4 H), 3.90 (m, 2 H), 6.84 (s, 1 H), 7.21-7.35 (m, 5 H), 7.83 (dd, J = 4.5 Hz, 1.5 Hz, 2 H), 8.72 (dd, J = 4.5 Hz, 1.5 Hz, 2H).

Example 4: Synthesis of 3-benzyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one (Compound No. 69 in Table-1)

Melting Point: 86-88 ℃.

NMR ($CDCl_3$, δ): 2.15 (m, 2 H), 2.68-2.75 (m, 4 H), 5.26 (s, 2 H), 6.95 (s, 1 H),

7.05-7.15 (m, 4 H), 7.21-7.31 (m, 6 H), 7.86 (dd, J = 4.5 Hz,1.5 Hz, 2 H), 8.72 (dd, J = 4.5 Hz, 1.5 Hz, 2H).

Example 5: Synthesis of 3-methyl-2-phenyl-6-(4-pyridyl)-3*H*- pyrimidin-4-one (Compound No. 41 in Table-1).

Melting Point: 181-182 ℃.

NMR ($CDCl_3$, δ): 3.53 (s, 3 H), 6.98 (s, 1 H), 7.74-7.63 (m, 5 H), 7.85 (dd, J = 4.6 Hz, 1.5 Hz, 2 H), 8.73 (dd, J = 4.6 Hz, 1.5 Hz, 2H).

Example 6: Synthesis of 3-(3-aminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one (Compound No. 74 in Table-1)

Melting Point: 197-200 ℃.

Example 7: Synthesis of 3-(3-aminopropyl)-2-(4-phenylbutyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one (Compound No. 84 in Table-1)

Melting Point: 150-153 ℃.

Example 8: Synthesis of 3-(3-aminopropyl)-2-(3-(2-methoxyphenyl)propyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one

Melting Point: 168-172 ℃.

Example 9: Synthesis of 3-methyl-2-(3-hydroxy-3-phenylpropyl)-6-(4-pyridyl)-3*H*-pyrimidin-4-one

Melting Point: 166-169 ℃.

Test Example: Inhibitory activity of the medicament of the present invention against

P-GS1 phosphorylation by bovine cerebral TPK1:

A mixture containing 100 mM MES-sodium hydroxide (pH 6.5), 1 mM magnesium acetate, 0.5 mM EGTA, 5 mM β-mercaptoethanol, 0.02% Tween 20, 10% glycerol, 12 μg/ml P-GS1, 41.7 μM [γ-^{32}P] ATP (68 kBq/ml), bovine cerebral TPK1 and a compound shown in Table (a final mixture contained 1.7% DMSO deriving from a solution of a test compound prepared in the presence of 10% DMSO) was used as a reaction system. The phosphorylation was started by adding ATP, and the reaction was conducted at 25°C for 2 hours, and then stopped by adding 21% perchloric acid on ice cooling. The reaction mixture was centrifuged at 12,000 rpm for 5 minutes and adsorbed on P81 paper (Whatmann), and then the paper was washed four times with 75 mM phosphoric acid, three times with water and once with acetone. The paper was dried, and the residual radioactivity was measured using a liquid scintillation counter. The IC_{50} values of eight compounds described in Example 1,2,3,4,6,7,8 and 9 were less than 5 μM. The test compound markedly inhibited the P-GS1 phosphorylation by TPK1. The results strongly suggest that the medicaments of the present invention inhibit the TPK1 activity, thereby suppress the Aβ neurotoxicity and the PHF formation, and that the medicaments of the present invention are effective for preventive and/or therapeutic treatment of Alzheimer disease and the above-mentioned diseases.

Formulation Example

(1) Tablets

The ingredients below were mixed by an ordinary method and compressed by using a conventional apparatus.

Compound of Example 1	30 mg
Crystalline cellulose	60 mg

Corn starch	100 mg
Lactose	200 mg
Magnesium stearate	4 mg

(2) Soft capsules

The ingredients below were mixed by an ordinary method and filled in soft capsules.

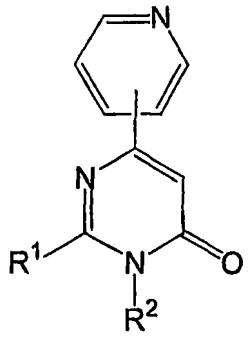
Compound of Example 1	30 mg
Olive oil	300 mg
Lecithin	20 mg

Industrial Applicability

The compounds of the present invention have TPK1 inhibitory activity and are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of diseases caused by abnormal advance of TPK1 such as neurodegenerative diseases (e.g. Alzheimer disease) and the like.

CLAIMS

1. A 3-substituted-4-pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:



(I)

wherein R^1 represents a C_1-C_{18} alkyl group which may be substituted or a C_6-C_{14} aryl group which may be substituted;

R^2 represents a C_1-C_{18} alkyl group which may be substituted or a C_7-C_{20} aralkyl group which may be substituted.

2. The 3-substituted-4-pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 1, wherein R^1 is a C_1-C_{18} alkyl group which is substituted by amino group, a C_1-C_5 monoalkylamino group, a C_2-C_{10} dialkylamino group, hydroxyl group or a phenyl group which may be substituted; or phenyl group which may be substituted

3. The 3-substituted-4-pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 2, wherein R^2 is a C_1-C_{10} alkyl group which may be substituted by amino group, a C_1-C_5 monoalkylamino group, or a C_2-C_{10} dialkylamino group; or C_7-C_{20} aralkyl group which may be substituted.

4. The 3-substituted-4-pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 3, wherein R^1 is a C_1-C_{10} alkyl group which is substituted by amino group, a C_1-C_5 monoalkylamino group, or

phenyl group which may be substituted.

5. The 3-substituted-4-pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 4, wherein R^2 is a C_1-C_5 alkyl group which may be substituted by amino group, a C_1-C_5 monoalkylamino group, or a C_2-C_{10} dialkylamino group; or benzyl group which may be substituted.

6. The 3-substituted-4-pyrimidone derivative or the salt thereof, or the solvate thereof or the hydrate thereof according to claim 5, wherein the pyridyl group bound to the pyrimidine ring in formula (I) is unsubstituted-4-pyridyl group.

7. A 3-substituted-4-pyrimidone derivative which is selected from the group consisting of:

3-methyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-ethyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

2-(3-phenylpropyl)- 3-propyl-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-benzyl-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-aminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-methylaminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-dimethylaminopropyl)-2-(3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-aminopropyl)-2-(4-phenylbutyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-(3-aminopropyl)-2-(3-(2-methoxyphenyl)propyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

3-methyl-2-(3-hydroxy-3-phenylpropyl)-6-(4-pyridyl)-3*H*- pyrimidin-4-one

or a salt thereof, or a solvate thereof or a hydrate thereof

8. A medicament comprising as an active ingredient a substance selected from the group consisting of a 3-substituted-4-pyrimidone derivative represented by formula (I) or a salts thereof, or a solvate thereof or a hydrate thereof according to claim 1.

9. A tau protein kinase 1 inhibitor selected from the group of a 3-substituted-4-pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 1.

10. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity.

11. The medicament according to claim 8 which is used for preventive and/or therapeutic treatment of a neurodegenerative disease.

12. The medicament according to claim 11, wherein the disease is selected from the group consisting of Alzheimer disease, ischemic cerebrovascular accidents, Down syndrome, cerebral bleeding due to cerebral amyloid angiopathy, progressive supranuclear palsy, subacute sclerosing panencephalitic parkinsonism, postencephalitic parkinsonism, pugilistic encephalitis, Guam parkinsonism-dementia complex, Lewy body disease, Parkinson's disease, tauopathies, vascular dementia, cerebrovascular accidents, traumatic injuries, peripheral neuropathies, retinopathies, and glaucoma.

13. The medicament according to claim 8, which is used for preventive and/or therapeutic treatment of non-insulin dependent diabetes and obesity; manic depressive illness; schizophrenia; alopecia; or a cancer.

14. The medicament according to claim 13, wherein the cancer is breast cancer, non-small cell lung carcinoma, thyroid cancer, T-cell leukemia, B-cell leukemia or a virus-induced tumor.

15. A method for preventive and/or therapeutic treatment of a disease caused by tau protein kinase 1 hyperactivity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) according to claim 1 and a physiologically acceptable salt thereof, and a solvate thereof and a hydrate thereof.

16. A use of a substance selected from the group consisting of the 3-substituted-4-pyrimidone derivative of formula (I) according to claim 1 and a physiologically acceptable salt thereof, and a solvate thereof and a hydrate thereof for

the manufacture of the medicament according to claim 8.